Journal of the American College of Cardiology
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Published by Elsevier Science Inc.

Vol. 39, No. 8, 2002
ISSN 0735-1097/02/$22.00
PII S0735-1097(02)01763-1

Angiotensin II Receptor Blockade Does Not Improve Left Ventricular Function and Remodeling in Subacute Mitral Regurgitation in the Dog

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OBJECTIVES We hypothesized that angiotensin II type-1 (AT_1) receptor blocker (AT_1RB) would prevent adverse left ventricular (LV) remodeling and LV dysfunction when started at the outset of mitral regurgitation (MR).

BACKGROUND Little is known regarding the efficacy of AT_1RB treatment of MR.

METHODS Mitral regurgitation was induced by chordal disruption in adult mongrel dogs. Six normal dogs (NLs) were compared to six untreated MR dogs (MR) and seven dogs treated with the receptor blocker irbesartan (MR+AT_1RB) started 24 h after induction of MR (60 mg/kg p.o. b.i.d.) and continued for three months.

RESULTS Treatment with AT_1RB decreased systemic vascular resistance but did not significantly improve cardiac output, LV end-diastolic dimension (LVEDD) or LVEDD/wall thickness compared to untreated MR dogs. Resting isolated cardiomyocyte length increased in MR versus NLs and was further increased in AT_1RB dogs. Left ventricular end-systolic dimension increased to a greater extent from baseline in AT_1RB dogs versus untreated MR dogs ($29 \pm 9\%$ vs. $12 \pm 6\%$, $p < 0.05$), despite a significantly lower LV peak systolic pressure in AT_1RB dogs. Plasma-angiotensin (ANG) II was elevated greater than threefold in both MR and MR+AT_1RB versus NLs. In contrast, intracardiac ANG II was increased greater than twofold in MR dogs versus NLs, but was normalized by AT_1RB.

CONCLUSIONS The use of AT_1RB decreased systemic vascular resistance and attenuated local expression of the renin-angiotensin system but did not prevent adverse LV chamber and cardiomyocyte remodeling. These results suggest that blockade of the AT_1 receptor does not improve LV remodeling and function in the early myocardial adaptive phase of MR. (J Am Coll Cardiol 2002;39:1374–9) © 2002 by the American College of Cardiology Foundation

Chronic hemodynamic stress results in neurohormonal activation that can lead to adverse cardiac remodeling and congestive heart failure (CHF), both by an adverse effect of systemic hemodynamics, and by a direct effect on the myocardium. Blockade of the renin-angiotensin system (RAS) with angiotensin-converting enzyme (ACE) inhibitors has been demonstrated to modulate adverse left ventricular (LV) remodeling and beneficially alter the natural history in experimental animal models as well as in clinical trials of CHF. The underlying etiology of heart failure cardiomyopathy in the major ACE inhibitor clinical trials has predominantly been coronary disease, hypertension or idiopathic. There is surprisingly little information regarding the long-term efficacy of RAS inhibition in CHF due to pure valvular incompetence, as patients with primary valvular incompetence have been consistently excluded from the large randomized ACE inhibitor and angiotensin II type-1 receptor blocker (AT_1RB) trials of heart failure (1–6).

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We have recently reported that chronic treatment with the ACE inhibitor ramipril 10 mg b.i.d. failed to attenuate adverse LV remodeling or the increase in cardiomyocyte length in dogs with chronic mitral regurgitation (MR) (7), despite a decrease in pulmonary capillary wedge pressure and reduction of LV angiotensin (ANG) II levels to normal. The reason for the failure of ACE inhibitors to prevent adverse remodeling in chronic MR, despite normalization of tissue ANG II and in contrast to the beneficial effects of these agents in multiple other etiologies of CHF, is uncertain. The LV ANG II levels were decreased, but not below normal levels in the MR dogs, possibly owing to the presence of chymase in the dog heart. Furthermore, angiotensin II type-1 (AT_1) receptor expression increased significantly with chronic ACE inhibitor treatment (7), raising the possibility of an enhanced action of ANG II in the presence of normal tissue stores. In the current study, we test the hypothesis that AT_1 receptor blockade favorably influences LV chamber and cardiomyocyte function and remodeling in dogs with chronic MR induced by chordal disruption.

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Manuscript received December 31, 2000; revised manuscript received December 13, 2001, accepted January 30, 2002.

Abbreviations and Acronyms

ACE	= angiotensin-converting enzyme
ANG	= angiotensin
ANOVA	= analysis of variance
AT_1	= angiotensin II type-1 receptor
AT_2	= angiotensin II type-2 receptor
AT_1RB	= angiotensin II type-1 receptor blocker
CHF	= congestive heart failure
LV	= left ventricle/ventricular
LVEDD	= left ventricular end-diastolic dimension
LVESD	= left ventricular end-systolic dimension
LVESS	= left ventricular end systolic stress
LVESV	= left ventricular end systolic volume
MR	= mitral regurgitation
NL	= normal dogs
RAS	= renin-angiotensin system

METHODS

Experimental preparation. Mitral regurgitation was induced at Auburn University College of Veterinary Medicine (Auburn, Alabama) in conditioned mongrel dogs of either gender (19 to 26 kg) by chordal rupture using a fluoroscopic guided catheterization method previously described in our laboratory (7,8). Dogs were randomly assigned to one of three groups: 1) three months of chronic MR (n = 6); 2) three months of chronic MR and treatment with the AT_1 receptor antagonist (irbesartan, 60 mg/kg p.o., twice daily; n = 7) starting 24 h after MR induction; and 3) unoperated controls (n = 6). We have previously demonstrated that irbesartan given 30 mg/kg p.o. b.i.d. for three days produced a 70% inhibition of ANG II pressor response 6 h after the last dose. A dose of 60 mg/kg p.o. b.i.d. achieved a 70% depression of ANG II pressor response at 12 h after the last dose (9). In the current proposal, doses were titrated up to 60 mg/kg p.o. b.i.d. as systemic blood pressure permitted.

At the conclusion of the study period, the dogs were transferred to the Medical University of South Carolina at Charleston where echocardiography and catheterization were performed prior to sacrifice. This study was approved by the Animal Services Committees at the University of Alabama at Birmingham, Auburn University College of Veterinary Medicine and the Medical University of South Carolina at Charleston.

Terminal catheterization study. Two-dimensional and M-mode echocardiography (ATL Ultramark VI, 2.25 MHz transducer, Bothell, Washington) were used to image the LV from a right parasternal approach (10). Electrocardiographic monitoring was established and the dogs anesthetized as previously described (7,8). A multilumen thermodilution catheter (7.5F, Baxter Healthcare, Irvine, California) was inserted into the left jugular vein and positioned in the pulmonary artery for measurement of thermodilution cardiac output and for pulmonary artery and pulmonary capillary wedge pressures. A precalibrated 7F micromanometer catheter (PPG Biomedical Systems, Pleasantville, New York) was advanced through the left carotid artery into the LV. A fluid-filled 7F catheter was advanced into the abdominal aorta from the right femoral artery for aortic pressure measurements.

The LV fractional shortening was calculated from the echocardiographic measurements as: (end-diastolic dimension − end-systolic dimension)/end diastolic dimension (%). The LV peak and end-systolic (defined at peak − dP/dt) circumferential wall stress was computed using a spherical model:

$$\sigma(g/cm^2) = (PD/4\ h\ [1 + h/D]) \times 1.36$$

where P = systolic blood pressure, D = minor axis dimension and h = wall thickness (10). The LV forward stroke volume was computed as the thermodilution cardiac output/heart rate. The LV regurgitant fraction (%) was computed as: (echocardiographic-determined stroke volume − thermodilution stroke volume)/echocardiographic stroke volume. Echocardiographic volumes were computed based upon previously validated formulae for dogs in both the normal and MR state (10).

Following the catheterization measurements, a sternotomy was performed, and the heart quickly extirpated, placed in a phosphate-buffered ice slush and the coronaries flushed with oxygenated Krebs solution. The great vessels were removed at the aortic and pulmonary valves and the right ventricle and LV quickly weighed. The LV was cut into 1 × 1 × 1-cm cubes and snap-frozen in liquid nitrogen for subsequent biochemical studies. The region of the LV free wall incorporating the circumflex artery (5 × 5 cm) was excised and prepared for myocyte isolation. Left ventricular myocytes were harvested using techniques described previously (9).

CARDIAC ANG II CONCENTRATIONS. Plasma and cardiac ANG II concentrations were determined as previously described from our laboratory by a method that combines solid-phase extraction, high-performance liquid chromatography and radioimmunoassay (7,8).

CARDIAC ACE AND CHYMASE ACTIVITIES. Cardiac ACE activity was measured with an assay developed in our laboratory, which uses the ACE-specific artificial substrate hippuryl histidyl leucine and quantifies the product hippuric acid by ultraviolet detection at 228 nm (7,8,11). The ACE is extracted from homogenized cardiac tissue with detergent, and the reaction product hippuric acid is isolated from the reaction mixture by reverse-phase HPLC, thus eliminating interference from the detergent, the ACE-specific substrate hippuryl histidyl leucine, and unreacted reaction by-products.

Chymase activity was assayed as previously reported by our laboratory (7,8). Generated ANG II was quantitated using a Reversed-Phase Alltima 5-μm phenyl-HPLC column (Alltech, Deerfield, Illinois). The peak area corresponding to a synthetic ANG II standard was integrated to calculate ANG II formation. Chymostatin-inhibitable ANG II formation was considered to represent the

Table 1. Left Ventricular Function and Hemodynamics in MR: Effect of AT_1RB

	NL	MR	MR+ AT_1RB
Heart rate (beats/min)	111 ± 9	105 ± 6	108 ± 7
Mean arterial pressure (mm Hg)	96 ± 5	92 ± 7	77 ± 3*†
Mean pulmonary artery pressure (mm Hg)	7.3 ± 0.9	14.1 ± 3.0*	12.0 ± 1.6
Pulmonary capillary wedge pressure (mm Hg)	4.8 ± 0.6	11.7 ± 2.2*	8.7 ± 1.6
Total systemic resistance (dyne·s·cm^{-5})	2673 ± 651	4675 ± 707*	2728 ± 326†
Cardiac output (l/min)	3.9 ± 1.0	1.8 ± 0.4*	2.5 ± 0.3
LV forward stroke volume (ml)	33.9 ± 6.2	16.9 ± 2.5*	23.0 ± 2.4*
Regurgitant stroke volume (ml)	—	54 ± 8	59 ± 13
LV mass to body weight ratio (g/kg)	4.1 ± 0.5	6.7 ± 0.4*	5.9 ± 0.5*
Cardiomyocyte length (μm)	144.5 ± 0.7	164.9 ± 0.8*	173.7 ± 0.8*†
LV fractional shortening (%)	43 ± 3	45 ± 2	42 ± 4
LVEDD (cm)	3.7 ± 0.1	5.1 ± 0.1*	5.3 ± 0.3*
LVESD (cm)	2.1 ± 0.1	2.8 ± 0.1*	3.1 ± 0.3*
LV end-diastolic volume (ml)	44 ± 4	99 ± 7*	116 ± 17*
LVESV (ml)	12 ± 1	25 ± 3*	35 ± 6*
LV ejection fraction (%)	72 ± 3	75 ± 2.1	71 ± 4
LV end-diastolic wall thickness (cm)	1.02 ± 0.03	0.71 ± 0.02*	0.75 ± 0.02*
LVEDD/LV wall thickness ratio	3.6 ± 0.1	7.3 ± 0.3*	7.1 ± 0.3*
LV peak systolic pressure (mm Hg)	123 ± 3	116 ± 8	101 ± 4*†
LV end-diastolic pressure (mm Hg)	4.8 ± 0.8	9.9 ± 1.3*	8.0 ± 1.4*
Maximum + LV dP/dt (mm Hg/s)	2,309 ± 227	1,717 ± 193*	1,688 ± 68*
LV peak systolic wall stress (g/cm^2)	121 ± 4	253 ± 24*	217 ± 17*
LV end systolic wall stress (g/cm^2)	26.1 ± 4.9	39.3 ± 5.2	39.0 ± 7.1
LVESS/LVESV ratio (g/cm^2/cc)	2.4 ± 0.4	1.7 ± 0.1	1.3 ± 0.2*
LV end-diastolic wall stress (g/cm^2)	5 ± 1	21 ± 3*	18 ± 3*
Sample size (n)	6	6	7

*$p < 0.05$ vs. Control. †$p < 0.05$ vs. MR. Values presented as mean ± SEM.

AT_1RB = angiotensin type-1 receptor blocker; LV = left ventricle/ventricular; LVEDD = left ventricular end-diastolic dimension; LVESD = left ventricular end-systolic dimension; LVESS = left ventricular end-systolic stress; LVESV = left ventricular end-systolic volume; MR = mitral regurgitation; NL = normal dogs.

chymase-like activity, expressed as nanomoles of ANG II formed per minute per gram of tissue (wet wt).

Data analysis. Indices of LV function, systemic hemodynamics and biochemistry were compared among the treatment groups using analysis of variance (ANOVA). If the ANOVA revealed significant differences, pairwise tests of individual group means were compared using Bonferroni probabilities. For comparisons of neurohormonal profiles, the Student-Newman-Keuls test was employed. The treatment effects were MR and drug therapy. Each dog was considered a complete block. All statistical procedures were performed using the BMDP statistical software package (BMDP Statistical Software, Los Angeles, California). Results are presented as mean ± SEM. Values of $p < 0.05$ were considered to be statistically significant.

RESULTS

Hemodynamics. Systemic vascular resistance was increased twofold in untreated MR dogs. The AT_1RB decreased systemic vascular resistance to normal levels ($p < 0.05$, MR vs. MR+AT_1RB). Cardiac output was significantly decreased in untreated MR dogs versus normal dogs (NLs) ($p < 0.05$) but did not differ in MR+AT_1RB versus NLs. Mean pulmonary artery pressure and pulmonary capillary wedge pressure were likewise significantly elevated in MR dogs compared to NLs and intermediate in MR+AT_1RB dogs.

Left ventricular mass/body weight was increased in both MR and MR+AT_1RB compared to NLs. The LV mass/body weight was less in the MR+AT_1RB versus MR dogs, but this did not achieve statistical significance. The LV end-diastolic dimension (LVEDD), LV end-diastolic volume, LVEDD/wall thickness ratio and LV end-diastolic wall stress increased to a similar extent in the untreated MR and MR+AT_1RB dogs compared to NLs. In parallel with the eccentric LV chamber remodeling, resting cardiomyocyte length was increased in both MR and MR+AT_1RB dogs compared to NLs (164.9 ± 0.8 μm and 173.7 ± 0.8 μm versus 144.5 ± 0.7 μm, respectively, $p < 0.05$, Table 1). However, cardiomyocyte length was greater in the MR+AT_1RB compared to MR dogs ($p < 0.05$).

Left ventricular peak positive dP/dt was significantly depressed in both MR and MR+AT_1RB dogs compared to NLs. Both LV end-systolic dimension (LVESD) and LV end-systolic volume (LVESV) increased significantly with MR in both groups; however, there was a trend toward a greater increase in LVESV in MR+AT_1RB versus MR dogs ($p = 0.05$). This trend, coupled with a LV peak systolic pressure that was significantly lower in MR+AT_1RB dogs, suggested greater contractile depression in MR+AT_1RB dogs. Similarly, the LV end-systolic stress (LVESS)/LVESV ratio was significantly depressed in the MR+AT_1RB versus NLs ($p < 0.05$). The LVESS/LVESV depression was intermediate in untreated MR dogs, com-

Table 2. Change From Baseline in Echocardiograph-Derived Parameters

	Baseline	3 Months	% Change
LVEDD (cm)			
MR	3.8 ± 0.1	5.1 ± 0.1†	32.9 ± 4.9†
MR+AT_1RB	3.8 ± 0.2	5.3 ± 0.3†	40.2 ± 8.9†
LVESD (cm)			
MR	2.6 ± 0.1	2.8 ± 0.1	12.2 ± 5.9*†
MR+AT_1RB	2.6 ± 0.2	3.1 ± 0.3†	28.9 ± 8.8*†
Fractional shortening (%)			
MR	33.5 ± 2.7	45.4 ± 1.9†	40.2 ± 13.6†
MR+AT_1RB	32.8 ± 2.1	41.8 ± 3.8†	27.2 ± 7.0†

*$p < 0.05$ vs. MR. †$p < 0.05$ vs. baseline. Values presented as mean ± SEM.
AT_1RB = angiotensin II type-1 receptor blocker; LVEDD = left ventricular end-diastolic dimension; LVESD = left ventricular end-systolic dimension; MR = mitral regurgitation.

pared to NLs and MR+AT_1RB ($p < 0.10$ for MR vs. NLs, and MR vs. MR+AT_1RB).

To correct for potential baseline differences in LV chamber size between groups, the percent change in LV chamber dimensions from baseline to three months was calculated for MR and MR+AT_1RB dogs (Table 2). Baseline LVEDD, LVESD and fractional shortening did not differ significantly between MR and MR+AT_1RB dogs. Percent changes in LVEDD (33 ± 5 vs. 40 ± 9% increase) and in fractional shortening (40 ± 14 vs. 27 ± 7% increase) did not differ in MR versus MR+AT_1RB dogs. However, LVESD increased to a greater extent from baseline in MR+AT_1RB versus MR dogs (29 ± 9 vs. 12 ± 6%, $p < 0.05$). Taken together, AT_1RB did not improve function or remodeling despite reductions in blood pressure and systemic vascular resistance.

LV ACE and chymase activity, ANG peptide levels and plasma renin activity. Plasma renin activity and plasma ANG I and ANG II increased threefold in MR and fivefold in MR+AT_1RB dogs (Fig. 1). The LV ANG II levels were increased twofold in MR compared to NLs ($p < 0.05$) but decreased significantly in MR+AT_1RB dogs to levels not significantly different from NLs (Fig. 2). Left ventricular midwall ACE activity increased more than twofold in MR versus NLs ($p < 0.05$) and decreased in MR+AT_1RB to levels not significantly different from NLs (Fig. 2). Chymase activity did not differ among groups.

DISCUSSION

The unique findings of this study were that AT_1RB, which was initiated immediately after induction of MR and continued throughout the ensuing three months, failed to prevent LV hypertrophy, eccentric LV remodeling and elongation of cardiomyocytes. Further, there was evidence of a greater percent increase in LVESD and greater elongation of cardiomyocytes in the dogs treated with AT_1RB compared with untreated MR dogs. Thus, AT_1RB decreased systemic vascular resistance and reduced local expression of the RAS but did not result in an improvement in LV function or remodeling.

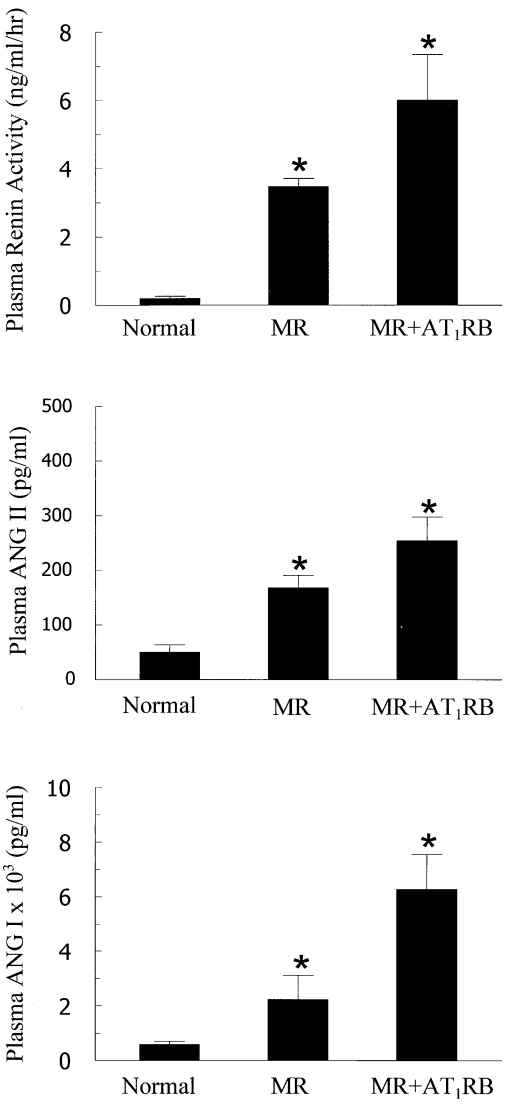

Figure 1. Plasma renin activity: angiotensin (ANG) I and ANG II levels are increased in mitral regurgitation (MR) and MR+AT_1RB compared to normal (NL) dogs. *$p < 0.01$ MR+AT_1RB and MR vs. normal dogs. AT_1RB = angiotensin II type-1 receptor blocker.

Cardiac RAS in MR. There was evidence of effective AT_1 receptor blockade both at the plasma and tissue levels. Plasma renin activity and plasma ANG II were elevated in MR dogs and increased further in the AT_1RB dogs, reflecting disinhibition of renin release by AT_1RB. In tissue, LV ACE activity and ANG II concentrations, both of which were elevated in MR dogs, were normalized by AT_1RB. Hemodynamic changes most likely do not account for the normalization of LV ACE, as the latter correlates most closely with diastolic wall stress (7), which did not differ significantly between MR and AT_1RB dogs. The angiotensin type-2 (AT_2) receptor knockout mice have increased tissue ACE activity (12), suggesting that stimulation of the AT_2 receptor inhibits tissue ACE formation. Thus, unopposed AT_2 receptor stimulation due to AT_1RB may account for the decrease in LV ACE in AT_1RB dogs.

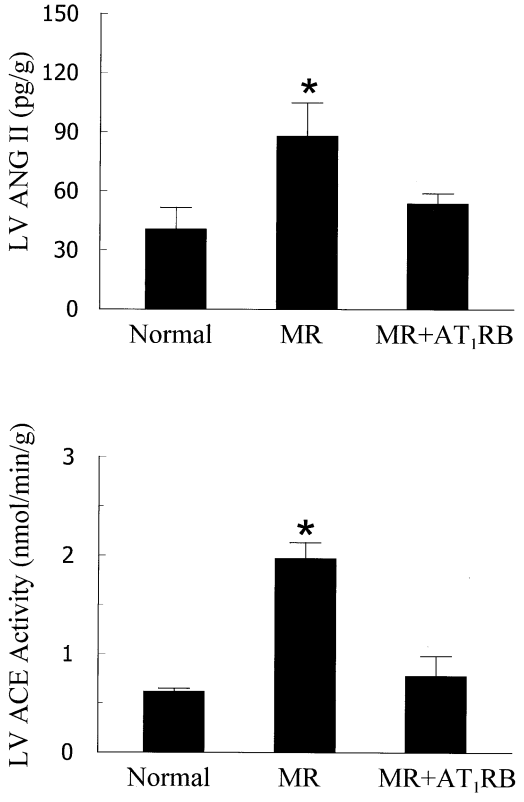

Figure 2. Left ventricular (LV) angiotensin (ANG) II concentrations and LV angiotensin-converting enzyme (ACE) activity levels in normal, mitral regurgitation (MR) and MR+AT_1RB dogs demonstrating that ANG II and ACE were increased greater than twofold in MR dogs vs. normals, but were normalized by AT_1RB. *$p < 0.05$ MR vs. normal dogs. AT_1RB = angiotensin II type-1 receptor blocker.

Decreased LV ACE activity may account in part for the decrease in LV ANG II.

In addition, recent studies have demonstrated that co-infusion of exogenous ANG II and AT_1RB in the normal intact pig (13) and in the isolated rat heart (14) results in lower tissue and interstitial fluid ANG II levels compared to infusion of ANG II alone. These findings are thought to be due to decreased cellular internalization of ANG II as a result of blockade of the AT_1 receptor, resulting in increased degradation of ANG II by extracellular peptidases. Thus, this mechanism may, in part, explain the normalized LV ANG II levels in MR+AT_1RB dogs.

Effect of RAS blockade in MR in humans. The failure to improve eccentric LV remodeling or LV function in AT_1RB dogs is certainly counterintuitive in the face of significant decreases in systemic vascular resistance and LV peak systolic pressure. However, clinical studies of chronic ACE inhibitor therapy in MR have also reported conflicting results. In a comprehensive review of these studies, Levine and Gaasch (15) concluded that the efficacy of ACE inhibitors in MR depended on their effect on regurgitant orifice area, which in turn depended on the underlying etiology of MR. They postulated that the observed efficacy of ACE inhibitor in papillary muscle dysfunction or dilated cardiomyopathy was due to a decrease in LV size and thereby in regurgitant orifice area as a result of afterload reduction. In contrast, ACE inhibitors were ineffective in rheumatic MR, which tends to have a fixed orifice area, and in mitral valve prolapse, a condition in which preload or afterload reduction may actually increase the prolapse and severity of MR (15). This could in part explain the failure of AT_1RB to reduce regurgitant volume and LV remodeling in our dogs with chordal rupture.

Effect of RAS blockade in dog model of MR. The LVESD increased to a greater extent from baseline in AT_1RB dogs versus untreated MR dogs, despite a significant reduction in systemic vascular resistance and LV peak systolic pressure. A previous study demonstrated that acute beta-blockade unmasked significant innate LV contractile depression after three months of MR in the dog (16). Thus, the adrenergic nervous system is extremely important in maintaining contractile function in the subacute phase of this canine model of MR. In the current investigation, AT_1RB was initiated within 24 h, most likely before steady-state myocardial compensation. In addition to its trophic effects on cardiomyocytes, ANG II has also been shown to have a positive myocardial inotropic effect either directly or indirectly via activation of AT_1 receptors on nerve terminals in the heart with subsequent release of norepinephrine (17). Indeed, we have recently shown that exogenous infusion of ANG II into the heart causes release of cardiac norepinephrine and epinephrine into the interstitial fluid space of the hearts of dogs in vivo, even in the absence of adrenal input (18). Thus, blockade of the AT_1 receptor may have prevented important inotropic support of the heart in the early adaptive phase of MR, thereby resulting in the discordance between the drug-mediated vasodilation and LV shortening.

In addition to the hemodynamic considerations noted in the preceding text, there are important morphometric features of MR that may account for the failure of ACE inhibitor and AT_1RB to prevent LV remodeling. The efficacy of the RAS blockade has been documented largely in clinical trials and in experimental animal models in the setting of postmyocardial infarction, hypertension or idiopathic dilated cardiomyopathy. In general, these conditions are characterized by increased collagen deposition in the extracellular matrix of the myocardium. The beneficial effects of RAS inhibition are mediated in part by suppression or reversal of this fibrosis (19). The canine model of MR, however, is characterized by an absence of fibrosis and by dissolution of the fine collagen weave (7). In fact, we found a tendency toward increased dissolution of collagen weave and increased cardiomyocyte length in the ACE-inhibitor-treated MR dogs, compared to untreated MR dogs (7). Loss of the fine collagen weave destroys the structural support of the extracellular matrix that is necessary for maintenance of normal LV chamber geometry and for the translation of forces from individual cardiomyocytes to the LV chamber (20). Thus, our failure to see a favorable effect of either AT_1RB or ACE inhibitor on LV remodel-

ing, myocyte lengthening or LV function following three months of MR may reflect an absence of fibrosis and pre-existing matrix degradation, in which RAS blockade may have a neutral or even deleterious effect.

Conclusions. Angiotensin II type-1 receptor blockade, which was begun shortly after the induction of MR, lowered systemic vascular resistance and decreased LV ANG II levels but did not improve LV remodeling or function in dogs in the early myocardial adaptive phase of MR. These results suggest that AT_1 receptor blockade may not be beneficial in patients who have recent onset of moderate to severe MR due to mitral valve prolapse.

Acknowledgments

The authors thank Angela C. Sampson, R. Brent New, Mark J. Clair and R. Stephen Krombach for their assistance in the isolated myocyte-function studies; Joan Durand for her performance of the radioimmunoassays; and Pamela Gibson for her expert secretarial skills in preparing the manuscript.

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